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The Effects of Body Mass Index on Hippocampal Volume in Women with Down Syndrome

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By

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Abstract

Individuals with Down Syndrome (DS) show significant development and aggressive progression of Alzheimer's disease (AD) at a significantly earlier age than neurotypical individuals. The risk of AD is also particularly high in women with DS; it is even higher than the risk of AD in neurotypical women, which in turn, is higher than the risk of AD in neurotypical men. The DS population, as a whole, has a lower hippocampal volume and a higher prevalence of obesity when compared to the neurotypical population. This study examined the relationship between BMI and hippocampal volumes in women with DS. MRI imaging, demographic data, and physical assessment data from women with DS aged 40-59 were obtained from the Alzheimer's Biomarker Consortium -Down Syndrome (ABC-DS) study database and were examined to evaluate the relationship between BMI and hippocampal volume. FreeSurfer was used to extract hippocampal volume from MRI images and BMI was calculated for each subject. The results suggested that BMI was not related to hippocampal volumes. However, ventricular volumes were negatively related to BMI suggesting that a higher BMI may be protective for the DS brain. Given the earlier onset and higher risk of AD in female subjects with DS and their higher prevalence of obesity, the data analyzed from subjects in this population may offer unique insight into the progression and risk of AD in women with DS.

Introduction

Alzheimer's Disease and Down Syndrome

Down Syndrome is a genetic disorder caused by the trisomy of the 21st chromosome (Wiseman et al., 2015). As a result of this trisomy, there is an extra copy of the gene encoding amyloid precursor protein (APP), a precursor to the neurotoxic protein amyloid beta (Aβ). APP is cleaved to form amyloid beta (Aβ), which instigates the progression of AD through the formation of amyloid cascade neuropathology (Schupf et al., 2018). This neuropathology is mainly characterized by neurofibrillary tangles, and high intracellular levels of the neurotoxic protein Aβ, directly resulting in the deposition of Aβ plaques. Aβ in its soluble and insoluble forms increases neuroinflammation, oxidative stress, and neuronal death; all of the aforementioned detriments are more prevalent in populations with DS, even before the definitive onset of AD neuropathology (Head et al., 2016). The higher prevalence of these factors is hypothesized to be a result of the dosage difference, caused by the extra copy of the APP gene. Consequently, populations with DS have a higher risk and earlier onset of AD (Schupf et al., 2006; Schupf et al., 2018).

In the general population of the U.S., there are 3.3 million cases of AD in women and a total of 5.2 million cases of AD, meaning that women constitute approximately two thirds of the total AD population (Pike, 2017; Oveisgharan et al., 2018). The reason for the imbalance in cases is still unclear, though it may be due to a combination of factors including women's loss of estrogen at menopause, their longer life expectancy, and their increased levels of tau tangles (Oveisgharan et al., 2018). AD in populations with DS is different from AD in neurotypical populations in that there is no sex difference involved in risk of AD in DS populations (Wiseman et al., 2015). These aberrancies between DS and neurotypical populations with AD may be due

to the duplication of the 21st chromosome which causes inherent hormonal and cardiovascular differences in people with DS (Schupf et al., 2006; Schupf et al., 2003; Wiseman et al., 2015).

The research findings are unclear regarding the timeline of AD progression in DS individuals. Lott and Head (2019) conducted a study in which nearly all individuals with DS developed neuropathological changes indicative of AD by the age of 40 (Lott & Head, 2019; Rubenstein et al., 2020). Conversely, a 2015 study conducted by Wiseman et. al, stated that, at the age of 40, less than 5% of individuals with DS had developed AD. Furthermore, from the age of 40-60, the risk of developing AD doubles every five years (Wiseman et al., 2015). Lastly, a study from Annus et al. (2017) claimed that the onset of AD neuropathology generally occurred at the age of 50 (Annus et al. 2017). While there is still debate about the exact age of onset, it is clear that age is a major risk factor for AD in people with DS, beyond what is seen in neurotypical populations.

Down Syndrome in AD and Hippocampal Volume

As the AD process causes widespread atrophy in the brain, one of the key targets for pathophysiological change is the hippocampus, a location vital to memory and learning (Laakso et al., 2000). Hippocampal atrophy begins early in AD, particularly at its frequent point of origination in the entorhinal and trans-entorhinal cortices (Raji et al., 2009). In early AD, the majority of the atrophy affects the anterior hippocampal horn, a portion heavily implicated in memory processing (Ho et al., 2011; Laakso et al., 2000). Later in the disease progression, the posterior hippocampus becomes the primary site of atrophy.

Interestingly, even in the absence of AD neuropathology, DS has been associated with lower hippocampal volumes, as illustrated in Figure 1, and enlarged ventricles (Annus et a., 2017). The lateral ventricles are located in the vicinity of the hippocampus, while the inferior

portion of the lateral ventricle directly borders the lateral side of the hippocampus (Fogwe et al., 2021). Due to the proximity of the ventricles to the hippocampus, they may be useful as an indirect measure of hippocampal atrophy, general cortical atrophy, or both. The lower hippocampal volumes found in individuals with DS is not surprising, considering that populations with DS also have a lower total brain mass and volume, more shallow gyri and sulci, and fewer neurons in the adjacent temporal lobes (Dierssen, 2012; Ho et al., 2011). Due to the decreased size of these structures, it is important to note that changes in hippocampal volume may be more subtle due to lower overall brain volume in DS brains. Besides these inherent structural differences in the period before amyloid deposition, AD progression in DS populations is very similar to AD in the general population (Annus et al., 2017).

Estrogen and AD in Down Syndrome

Although there is no sex difference in AD risk in DS populations, women with DS may have an element of neuroprotection that is not present in men with DS (Tyrrell et al., 2001; Schupf et al., 2006). Endogenous bioavailable estrogen is one factor that may reduce the risk of AD and attenuate aggressive neurodegeneration. Estrogens have been known to have numerous neuroprotective effects and may be helpful in fighting the progression of AD (Schupf et al., 2006). The benefits of estrone, a type of estrogen, include protection against the toxicity of Aβ, activation and maintenance of neuronal health in the cholinergic system, anti-inflammatory and antioxidant properties, and the facilitation of the non-amyloidogenic metabolism of APP, a precursor to Aβ (Behl et al., 1995; Toran-Allerand et al., 1992; Xu et al., 1998; Hosoda et al., 2001).

The loss of estrogen in postmenopausal women and the ensuing cognitive decline is considered an indication of a correlation between bioavailable estrogen and cognition (Yaffe et

al., 2000; Schupf et al., 2018). Earlier menopausal events and lower levels of bioavailable estrogen have been shown to increase the risk of AD and to expedite its onset (Schupf et al., 2018). It is important to note that most women with DS experience an onset of AD decades earlier than neurotypical populations; the age of onset of AD in the general population is normally after 75 years old, while in populations with DS, it is often present around the age of 35. Similarly, women with DS enter menopause at an average age of 44-46 compared to the average age of 51 in neurotypical women (Schupf et al., 2006; Schupf et al., 2017). The shorter period of time between menopause and the onset of AD in DS populations may enable researchers to study the effects of menopausal events on the risk and onset of AD with a decreased confounding effect caused by age (Schupf et al., 2018).

Body Mass Index and AD in Down Syndrome

Body mass index (BMI) is a ratio between weight and height, often used as an indication of weight and health status (King, 2007; Schupf et al., 2006); it is another factor that has been linked to AD risk and prevention and has been positively correlated with levels of estrone and estradiol, another type of estrogen. As well as being indirectly linked to cognition through estrogens, BMI has been directly associated with cognition in a study involving postmenopausal women with DS (Patel et al., 2004). Subjects who were categorized as obese (BMI ≥ 30 kg/m^2) performed significantly better on tests of verbal memory and neuropsychological function than non-obese women (Patel et al., 2004; Caballero et al., 2019). Through its association with higher levels of endogenous estrogen and higher scores on tests of cognitive function, BMI is an important factor to consider in AD research.

BMI is an especially relevant factor in people with DS because they have a significantly higher incidence of obesity, and therefore, a higher BMI than the general population (Wong et

al., 2014). There is also a sex difference involving BMI in people with DS; the prevalence of obesity is 11% higher in women with DS than in men with DS (Wong et al., 2014). While the disparity between obesity in people with DS and the general population is predominantly due to environmental and lifestyle factors, people with DS also have physiological factors such as low muscle tone, low metabolism, and hypothyroidism that predispose them to obesity (Wong et al., 2014). While higher BMIs have been linked to higher levels of the endogenous estrogen which can foster healthy cognition and reduce AD risk, BMI has also been correlated with lower cardiovascular health, which is a risk factor for AD (Gustafson et al., 2003; Schupf et al., 2006; Wong et al., 2014). In addition to increasing the risk of AD, obese individuals will likely succumb to the characteristic neurodegenerative processes of AD more easily due to poor cardiovascular health (Ho et al., 2011). Women with DS have significantly earlier menopausal events and AD onset, along with higher BMIs and reduced hippocampal volumes (Annus et al., 2017; Schupf et al., 2003; Wong et al., 2014). Consequently, women with DS are an important population in which to study the interactions of BMI with AD risk and neuropathology.

While BMI has been linked to AD progression in DS populations, it has similar effects on AD progression in the neurotypical population, in addition to being associated with hippocampal volume. BMI is inversely correlated with hippocampal volume in the early stages of disease-related cognitive impairment in neurotypical adults, suggesting that obese individuals are more vulnerable to the disease process (Ho et al., 2011). This may be because of the detrimental effects of obesity on cardiovascular health, which leads to neurovascular insufficiency in both DS and neurotypical populations (Ho et al., 2011; Wong et al., 2014). An unhealthy cardiovascular system and the overall poor health that it leads to can allow the disease process to continue uninhibited and encourage hippocampal atrophy, specifically in the anterior portion (Ho

et al., 2011). In the later stages of AD, when the posterior hippocampus is the main target of atrophy, BMI is directly correlated with hippocampal volume in neurotypical individuals (Ho et al., 2011). While this seems to suggest that BMI is beneficial to fighting the AD process, there are a number of confounding factors; the more advanced stages of AD are associated with lower BMI, partially because of the effect that cognitive impairment has on eating habits, and partially because of a decline in self-care and caregiver intervention (Wang, 2002). Thus, the association between BMI and late hippocampal atrophy is not a reliable indication of BMI's effect on cognition in AD. Conversely, in the early stages of AD where the individual is mildly cognitively impaired, BMI seems to have a detrimental effect on the brain's defense against the progression of AD (Ho et al., 2011). Since BMI is correlated with hippocampal volume in the neurotypical population, it is possible that these two factors are also linked in the DS population.

The higher prevalence of obesity and AD in women with DS, and the association between BMI and hippocampal volume in neurotypical populations are characteristics that are pivotal to this study. Combined with the shorter time period between menopause and the onset of AD, women with DS are an important population in which to consider the effects of BMI on hippocampal volume. Research in women with DS presents a unique opportunity to gain insights into AD progression in a population that is disproportionately burdened with the disease and particularly vulnerable to its effects. I hypothesize that BMI will be negatively related to hippocampal volumes in women with DS.

Methods

This study analyzed demographic information, physical assessments, and neuroimaging data from 36 women from 40-59 years old with DS in the ABC-DS database. Data were requested from the ABC-DS study, which includes the Neurodegeneration in Aging Down Syndrome (NiAD) and Alzheimer's Disease in Down Syndrome (ADDS) study sites. These data had been collected 3-4 times periodically over the 5-year course of the study. The NiAD study had 180 subjects who were 25 years and older, while there were 220-225 adults who were 40 years and older in the ADDS study. In total, there was available data on at least 400 participants, and it was expected that approximately 200 subjects would be female. The height and weight values in the physical assessment data were used to calculate a BMI for each participant. The neuroimaging database was searched using the following specifications: Study=ABCDS, Age=25-75, Group=DS, Visit=Baseline, Weighting=T1, and Acquisition=3D. Once the 323 results were reviewed, 134 were chosen based on quality of the image. Subjects aged 40-75 were selected for volumetric analysis via Freesurfer software. The hippocampal volume of participants with a normal BMI (BMI $\geq$ 18.5-24.9 kg/m^2) was compared to participants with BMIs indicating overweight (BMI $\geq$ 25-29.9 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) individuals and ANOVA models were used to compare across the two groups. Correlations were run between subject hippocampal volume and BMI. P-values were obtained for each correlation. Descriptive statistics were obtained for the demographic data from the sample whose MRI data were processed with Freesurfer.

Results

The subjects were 36 women with DS aged 40-59 years. There was a total of 35 subjects (n=35) with both demographic data and FreeSurfer volumetric analysis data and one subject (n=1) with only the FreeSurfer data. The subject without associated demographic data was not included in the statistical analysis. Subjects were categorized as premenopausal or postmenopausal, and there were 16 premenopausal women and 19 postmenopausal women. The subjects were also categorized by their dementia status: no Mild Cognitive Impairment (MCI) and no dementia, MCI, and dementia. There were 29 study subjects in the no dementia and no MCI group, two subjects in the MCI group, and four subjects in the dementia group. The BMIs of the subjects ranged from 21.82-51.85 kg/m^2. Each BMI was categorized as normal (BMI ≥ 18.5-24.9 kg/m²), overweight (BMI ≥ 25-29.9 kg/m², or obese (BMI ≥ 30 kg/m²). There were three subjects with a normal BMI, 10 subjects with an overweight BMI, and 22 subjects with an obese BMI.

BMI and Hippocampal Volume

The relationship between BMI and hippocampal volume was examined. There were no correlations between BMI and the right hippocampus (r= .281, p=.10) or the left hippocampus (r=.191, p=.27). While BMI was not correlated to hippocampal volume, it was found to be correlated with the volumes of the right inferior lateral ventricle, (r=-.35, p=.04), left inferior lateral ventricle, (r=-.34, p=.04) and right lateral ventricle, (r=-.*38*, p=.03).

A one-way ANOVA test was utilized to compare the hippocampal volumes for subjects in each of the dementia status groups. The mean volumes of the right hippocampus (F(2,32) = 11.91, p=<.001), and left hippocampus, (F(2,32) = 7.36, p=.002) were significantly different

between dementia status groups. Descriptive statistics were obtained for each dementia status group and are presented in Table 1. The mean volumes show that both hippocampi were smaller in MCI and AD groups.

Regressions were run for both hippocampal volumes with age and BMI as predictors to account for the effects of both variables on hippocampal volumes. The overall model of age and BMI explained a significant amount of variance in left hippocampal volume, R^2=.25, $F(2,32)=5.39$, p=.01. BMI was not a significant predictor of left hippocampal volume, b=.11, $t(32)= 0.70$, p=.49. However, age was a significant predictor of left hippocampal volume, b=-.47, $t(32)=-3.04$ p=.01.

Similarly, the overall model of age and BMI explained a significant amount of variance in the right hippocampal volume R^2=.25, $F(2,32)=5.34$, p=.01. BMI did not significantly predict the volume of the right hippocampus, b=.21, $t(32)=1.34$, p=.19, and age was a significant predictor of right hippocampal volume, b=-.42, $t(32)=-2.71$ p=.01.

Menopause Status and Hippocampal Volume

Hippocampal volumes were compared between premenopausal and postmenopausal groups. An independent samples *t*-test found a significant difference between the premenopausal and postmenopausal groups in measures of left hippocampus ($t(33)=2.68$, p=.01), and right hippocampus ($t(33)=2.54$, p=.02). Descriptive statistics were also obtained; as shown in Table 2, premenopausal women showed consistently higher mean hippocampal volumes than postmenopausal women.

Discussion

The main finding of this study was that there were no relationships between BMI and hippocampal volume. However, there were a number of significant findings that may provide

insight into the mechanisms of age- and dementia-related brain changes in women with DS and provide future directions for AD research in DS populations.

Both BMI and hippocampal volume are important factors to consider in research on women with DS and AD. It was hypothesized that BMI would influence the volume of the hippocampus in a sample of middle-aged and older women with DS. The data did not support this hypothesis; the data suggested that BMI was not related to hippocampal volume. However, there may be an alternative explanation, given the conflicting interactions of BMI with AD risk and progression. It is possible that the cardiovascular benefits and detriments of high BMI neutralize each other, resulting in no net effect on AD (Schupf et al., 2006). An increased BMI has been associated with higher levels of endogenous estrogen and higher performances on measures of cognitive function in women with DS (Patel et al., 2004; Schupf et al., 2006). Yet high BMI has also been known to decrease cardiovascular health, which hinders the brain's ability to fight AD progression. Considering the fact that no relationship was found between BMI and hippocampal volume despite the many connections between AD progression and BMI, it is likely that these opposite effects of BMI balance each other out. As a result, there was no overall effect on hippocampal volume.

Due to their proximity to the hippocampus and enlargement during cortical atrophy in AD, ventricular volume may be used as an indirect measure of hippocampal and medial temporal region volume. When a correlation was run between BMI and ventricular volume, the volumes of both inferior lateral ventricles and the right lateral ventricle showed a negative correlation with BMI. As previously noted, hippocampal changes in individuals with DS may be more difficult to detect, due to their smaller hippocampi prior to any AD-induced atrophy (Annus et al., 2017). Since the lateral and inferior lateral ventricles are located in the vicinity of the

hippocampi, even subtle hippocampal atrophy might be suggested by larger ventricular volumes (Fogwe et al., 2021). The ventricular enlargement may be caused by the atrophy of other AD-related structures, but due to the proximity of the hippocampi and their consistent atrophy in early and advanced stages of AD, it is possible that general volume changes in this medial temporal region may have contributed to the ventricle enlargement found in this study. Furthermore, as AD progresses into the later stages, it is associated with both larger ventricles and a lower BMI (Thompson et al., 2004; Wang, 2002).

Hippocampal volumes were also examined across the three dementia status groups. The mean hippocampal volume was significantly different between the groups with no MCI or AD, MCI, and AD. The mean hippocampal volume was smaller in groups with a more advanced stage of dementia. These expected findings illustrate the increasing hippocampal atrophy that is a defining trait of AD. Therefore, the decreasing size in hippocampal volume across disease status shown by these data is completely consistent with the normal progression of AD.

Menopause status was also used to examine hippocampal volume of women with DS. There was a difference between the hippocampal volumes of pre-menopausal and postmenopausal women with DS. This was an expected finding considering that menopause status is a proxy measure for age and age is a prominent risk factor for AD (Wiseman et al., 2015).

Although there was no relationship between BMI and hippocampal volume, this finding may still inform future AD research in DS populations. In addition to hippocampal volume, this study examined the relationships between menopause, dementia status, and ventricular volume and BMI. Further studies with larger numbers of women with DS are likely to provide more

information about the relationships between BMI, brain volume, menopause, and dementia status.

Limitations

The reliability and implications of the results are limited by the sample size of the study. Due to the time constraints of this project and the time-intensive process of running the subjects through the FreeSurfer software, the sample size was small. However, power calculations showed that the sample size had sufficient statistical power to detect a correlation of 0.30. Continuing these analyses with the rest of the sample available in the ABC-DS database would be the first step in examining the relationship between structural brain imaging measures and BMI in women with DS.

Conclusion

There are still a plethora of unknowns concerning the interactions of BMI and AD neuropathology in DS populations. This study focused specifically on examining the relationship between hippocampal volume and BMI in women with DS. While no relationship was found between these two variables, a more severe dementia status was associated with smaller hippocampal volumes. Also, postmenopausal women had smaller hippocampal volumes than premenopausal women. These results are consistent with previous research and illustrate the normal progression of AD in people with DS. It is important to explore the other avenues that may account for neuropathological and clinical differences between AD in the general population and AD in people with DS. Information vital to AD prevention and treatment may lie in the comparison between these differing presentations of AD.

Future Directions

In addition to repeating this study with a larger sample size, there are a few areas for further study that may be useful in elucidating the relationship between BMI and AD in individuals with DS. One idea for further study is to examine the relationship of BMI and hippocampal volume in groups of subjects with varying stages of AD. Since BMI decreases in the later stages of AD, any correlation in that group would be expected, but it would be interesting to track any associations between BMI and hippocampal volume throughout the progression of AD. The sample size of this study was too small to carry out these analyses for each dementia status group. BMI and hippocampal volume could also be studied in men with DS. Without the neuroprotective effects of estrogen, as seen in women with DS, higher BMIs may be associated with lower hippocampal volumes.

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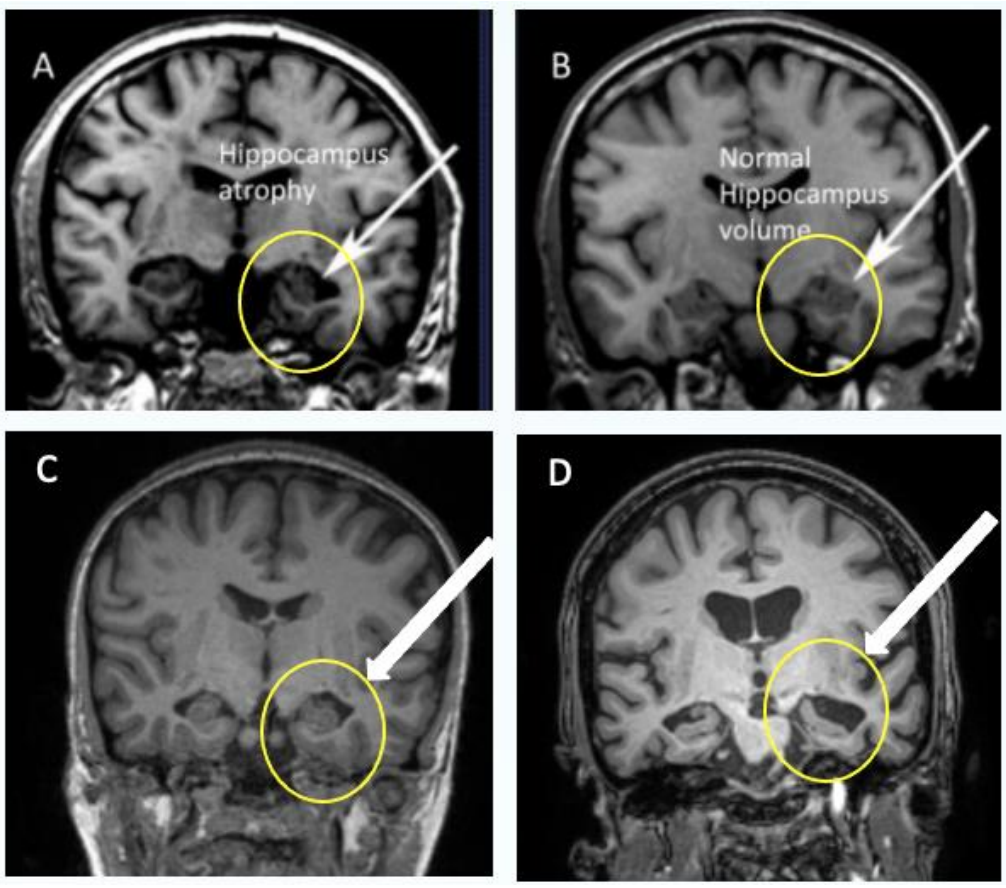
Figure Legend

Figure 1. Figure 1 shows four coronal slices of the brain at the level of the hippocampus. Figure 1a shows hippocampal atrophy in a neurotypical brain with AD. Figure 1b shows a normal hippocampus in a neurotypical brain. Figure 1c shows hippocampal atrophy in an ABC-DS subject with DS. Figure 1d shows hippocampal atrophy in an ABC-DS subject with DS and AD.

Figure 1.



Tables

Table 1. *The descriptive statistics for the comparison of hippocampal volumes and dementia status.*

Dementia Status	Right Hippocampal Volume	Left Hippocampal Volume
No MCI and No Dementia (0)	3240.3(453.6)	3010.9(421.5)
MCI (1)	2497.8(137.3)	2496.3(53.0)
Dementia (2)	2166.6(451.80)	2227.0(383.0)

Table 2. *The descriptive statistics for the comparison of hippocampal volumes between pre-menopausal and post-menopausal groups.*

Menopausal Status	Right Hippocampal Volume	Left Hippocampal Volume
Pre-menopausal (0)	3324.3(590.2)	3111.2(483.9)
Post-menopausal (1)	2865.4(477.2)	2707.2(406.9)